Correlation between High Serum Uric Acid Levels with Occurrence of Diabetic Peripheral Neuropathy in Patients with Type 2 Diabetes

Mudjiani Basuki[1], Muhammad Hamdan[1], Fidiana[1], Fadil[1], Deasy Putri Sukarno[1]

[1]Department of Neurology, Faculty of Medicine, Universitas Airlangga, Surabaya (60131), Indonesia

Abstract

Background: Diabetic Peripheral Neuropathy is a chronic microvascular complication of type 2 diabetes mellitus (T2DM) leads to increased risk of foot ulceration and morbidity.The increased serum uric acid (SUA) levels have been linked to macro vascular disease in T2DM. We found that the correlation between SUA levels and diabetic peripheral neuropathy has not been investigated.

Objective: To determine the correlation between high serum uric acid levels and diabetic peripheral neuropathy.

Method: The case-control design was used in this study and the sampling was done consecutively by following the inclusion and the exclusion criteria. The diabetic peripheral neuropathy was evaluated using EMNG and the serum were taken for uric acid levels examination. Chi square test was used for data analysis.

Results: Thirty subjects were enrolled and divided into an experimental group of 15 subjects and a control group of 15 subjects as well**.** We found that the diabetic peripheral neuropathy did not show a significant correlation with high serum uric acid levels, p=0,136 and OR 3,143 (CI 95% 0,681-14,503).

Conclusion: High serum uric acid levels did not have correlation with diabetic peripheral neuropathy.

Keywords: *High Serum, Neuropathy, Diabetes Melitus*

Introduction

Diabetes mellitus (DM) is a clinical syndrome characterized by hyperglycemia that occurs due to insulin secretion abnormalities, insulin performance, or both [1]. Type 2 Dibetes Mellitus (T2DM) is an increasing health problem of incidence and prevalence so it becomes a worldwide concern.[1-4] Diabetic Peripheral Neuropathy (DPN) is one of the most frequent chronic microvascular complications in T2DM.[3-5] Finger or foot infections and amputations are common risks faced by DPN. This causes an increase in morbidity and mortality resulting in increased medical costs of patients with DPN [2]. Prevalence of neuropathy in DM patients over 50% for 25 years. The overall prevalence of neuropathy was estimated at 30%. In the EURODIAB IDDM Complication Study, DPN is associated with blood glucose control and DM duration. Microvascular complications still occur, despite controlling of blood glucose levels was performed well (HbA1c 5.4% to 7%), so it is suspected other factors involved besides blood glucose control and duration of DM [3].

High serum uric acid (SUA) levels were associated with the incidence of macrovascular and microvascular complications in patients with DM.[11] Increased levels of SUA have been associated with endothelial dysfunction, ischemic heart disease, stroke, peripheral artery disease and death from cardiovascular disease.[3,12,13] In T2DM, the increased levels of SUA were associated with metabolic syndrome and insulin resistance. The association of high SUA levels with DM was reported in several studies. The association of hyperuricemia with DPN is still controversial [4]. The study by Ito et al (2011)

Corresponding Author:
Mudjiani Basuki
Department of Neurology, Faculty of Medicine,
Universitas Airlangga, Surabaya (60131), Indonesia
E-mail: mudjianibasuki@outlook.com

shows that DPN had a moderate significance (p <0.001) with a positive correlation (r=0.509) towards high SUA levels. Therefore, the purpose of this study was to determine the correlation between high serum uric acid levels and diabetic peripheral neuropathy.

Method

This study used a case control design with the population of all T2DM patients who visited to the endocrinology outpatient unit of Soetomo General Hospital and fulfilled the inclusion and the exclusion criteria during the period of August to December 2016. The inclusion criteria were 40-60 years old, EMNG results did not support the DPN and agreed to follow the research. While the exclusion criteria were chronic renal impairment, chronic liver disorder, history of malignancy, history of drug use and radiotherapy, history of alcohol consumption [5].

We used consecutive sampling as the sampling technique because it was the best non-probability sampling and easy to do. The sample size was determined using the formula of unpaired categorical analytic research. The value of the effect proportion on the control (P2) was determined based on the preliminary study and the calculation of the required minimum sample size was 15 people for each group [6].

The samples were divided into two groups; 15 subjects with EMNG results that did not support the diabetic neuropathy referred to as control group and 15 subjects with EMNG results that supported the diabetic neuropathy, hereinafter referred to as case/experimental group. The sampling conducted for 5 (five) months [7].

Additionally, the T2DM patients who fulfilled the inclusion and the exclusion criteria will be performed anamnesis, physical examination and then performed the blood tests for serum uric acid levels and other confounding factors. Statistical analysis was performed using SPSS 20.0 program. Collected categorical data were analyzed using Chi-Square test while numerical data were analyzed by T-test [8].

Result

The total subjects were 30 patients consisting of 15 subjects with EMNG results that did not support the DPN that referred to as control group and 15 subjects with EMNG results that supported the DPN, hereinafter referred to as case/experimental group. The basic characteristics of research subjects consisting of demographic and clinical data were showed in table 1. While the correlation between high serum uric acid levels and the incidence of diabetic peripheral neuropathy was shown in table 2.

Table 1. The Basic Characteristics of Subjects

Characteristics Experimental		**DPN Incidence**				**OR**
		Control	**Total**	**p**	**(CI 95%)**	
Sex						
-	Male	5 (33.3 %)	5 (33.3 %)	10 (33.3 %)	1.000	1.000
-	Female	10 (66.7 %)	10 (66.7 %)	20 (66.7 %)		(0.219-4.564)
Age		51.60+6,52	53.53+4.72		0.360	
Body Mass Index (BMI)						
-	Normal	9 (60.0 %)	9 (60.0 %)	18 (60.0 %)	1.000	1.000
-	Obesity	6 (40.0 %)	6 (40.0 %)	12 (40.0%)		(0.232-4.310)
Dyslipidemia						

Table 1. The Basic Characteristics of Subjects

-	Dyslipidemia	10 (66.7 %)	13 (867 %)	23 (76.7 %)	0.390	0.308
-	Normal	5 (33.3 %)	2 (13.3 %)	7 (23.3 %)		(0.049-1.928)
Hypertension						
-	Hypertension	4 (26.7 %)	6 (40.0 %)	10 (33.3 %)	0.439	0.545
-	Normal	11 (73.3 %)	9 (60.0 %)	20 (66.7 %)		(0.117-2.549)
Smoking						
-	Yes	1 (6.7 %)	1 (6.7 %)	2 (6.7 %)	1.000	1.000
-	No	14 (93.3 %)	14 (93.3 %)	28 (93.3 %)		(0.057-17.621)
Duration of Disease						
Type 2 Diabetes Mellitus						
-	≥ 5 years	12 (80.0 %)	2 (1.3 %)	14 (46.7 %)	0.000	0.038
-	< 5 years	3 (20.0 %)	13 (86.7%)	16 (53.3 %)		(0.005-0.271)
Serum HbA1c Levels						
-	High	12 (80.0 %)	10 (66.7 %)	22 (73.3 %)	0.682	0.500
-	Normal	3 (20.0 %)	5 (33.3 %)	8 (26.7 %)		(0.117-2.549)

Table 2. The Correlation between High Serum Uric Acid Levels and the Incidence of Diabetic Peripheral Neuropathy

		DPN Cases				**OR**
		Experimental	**Control**	**Total**	**p*)**	**(CI 95%)**
Serum Uric Acid Levels						
-	High	8 (53.3%)	4 (26.7%)	12 (40 %)	0.136	3.143
-	Normal	7 (46.7%)	11 (73.3 %)	18 (60 %)		(0.681-14.503)
Total		15 (100%)	15 (100%)	30 (100%)		

*) Pearson Chi-Square

Discussion

This study shows that there were no significant differences in basic variables consisting of demographic data. In addition we obtained that there were no significant differences in clinical data except the T2DM duration. Demographic data included age and sex while clinical data included BMI, dyslipidemia, hypertension, smoking, serum HbA1c levels and T2DM duration.

The mean age of the experimental group (51.60±6.52 years) was slightly younger than the control group (53.53±4.72 years), but this difference was not statistically significant with p=0.360. This result was in accordance with a study by Volmer et al that the mean age of samples that has suffering from DPN was 56.9±9.6 years [9]. But the mean age in this study was relatively young compared to the research that conducted by Wallace et al that the mean age of samples suffering DPN was 68.27±10.66 and the mean age that did not suffer DPN was 62.26±10.05 [10]. Multicenter studies conducted in the United Kingdom reported that the prevalence of diabetic peripheral neuropathy increases with age, from 5% (3.1-6.9%) in the 20-29 years age group to 44.2% (41.1-47.3%) in the 70-79 years age group. However, the samples over the age of 60 were not included in this study, because the age affects other types of neuropathy such as neuropathy due to vitamin deficiency, malnutrition, and others [11].

Characteristics of the subjects based on body mass index (BMI) in the experimental group were the subjects with normal BMI that was 9 patients (60.0%) meanwhile the subject of obesity in 6 patients (40.0%). However, this difference was not statistically significant with p=1,000. This was in accordance with a study that conducted by Koe et al., reported that there was also no significant difference between BMI and diabetic neuropathy (p=0.056) in 84 subjects. Obesity or combination with metabolic syndrome was a risk factor for neuropathy complications [12]. Obesity and triglycerides were associated with the loss of small axon nerves that were unveiled myelin.

Obesity was associated with edema that precedes the occurrence of clamp phenomena that disrupt the barrier so that nutritional deficiencies in susceptible nerve tissue. Obesity along with other metabolic syndromes leads to an increase in insulin resistance. T2DM and obesity have a complex relationship. Obesity was a precursor of T2DM via insulin resistance mechanism [13] Characteristics of the subjects based on the risk factor of dyslipidemia in the experimental group were found in 10 patients (66.7%) that less than the control group as many as 13 patients (86.7%).

Study conducted by Putri et al who found that dyslipidemia in the diabetic neuropathy group was 8% while in the diabetic neuropathy group was 44% with p=0.075 (p <0.001).[24] The study of dyslipidemia as a risk factor for neuropathy was still controversial. There was no significant difference between total cholesterol, HDL, LDL and triglyceride levels in people with type 2 DM who had somatic neuropathy with or without neuropathy. Patients with type 2 DM who were treated intensively with statins reduce the risk of autonomic neuropathy, but not DPN [14].

The different studies found that dyslipidemia was an independent risk factor for macro vascular disease in type 2 diabetes mellitus patients. In the preliminary study, decreased lipid levels with both fibrates and statins within 5 years prevented the incidence of new sensory neuropathy [3]. The decrease in lipid levels was performed using fibrate therapy (HR= 0.52; 95%; CI 0.27-0.98) and the use of statins therapy (HR = 0.65; 95% CI 0.46-0.93; p <0.042).[32] The results was consistent with the in vitro studies and animal studies that showed the levels of lipid-lowering therapy had the neuroprotective effects by improving the Schwann cells, polyol pathway, and the repair of nerve blood flow [2].

The characteristics of subjects based on hypertension in the experimental group found 4 patients (26.7%) with hypertension, then fewer than the control group that was 10 patients (40.0%). But in this study there was no statistically significant difference between the experimental and control group (p=0.439). West et al.'s study also found that there was no significant difference between the history of hypertension (p=0.124), systolic blood pressure (p=0.373), and diastolic blood pressure (p=0.640) with diabetic neuropathy. Hypertension was an independent factor in macro vascular disease, retinopathy, and nephropathy. Hypertension was a complication of blood vessels due to hyperinsulinemia. Insulin resistance increases sodium reabsorption in the proximal tubules of the kidney [15].

The characteristics of subjects based on smoking were 1 person (6.7%) who smoked in the experiment group while in the control group there were 14 people who did not (93.3%). But in this study there was no statistically significant difference between the experiment and control group (p=1.000). Additionally, the characteristics of subjects based on long-term T2DM ≥5 years in the case group was 12 people (80.0%) it was more than the control group that only 2 people (13.3%). While the subjects who suffer from DM <5 years in the case group was 5 people (20.0%), less than the control group that was 13 people (86.7%). The correlation test results showed that there was a correlation between the duration of DMT2 and the incidence of diabetic

peripheral neuropathy (p=0.000; odds ratio 0.038; 95% CI 0.005-0.271). This was consistent with some studies obtained a correlation between the duration of DM and diabetic neuropathy [16]. Research conducted by Fatkhur et al stated that the longer the patient suffering from DM, the risk of diabetic neuropathy was 16.7787 times greater in DM ≥5 years (p = 0.000). In addition to hyperglycemia, the duration of DM was a risk factor for DPN in Diabetes Control and Complications Trial.

Moreover, characteristics of the subjects by high serum levels of HbA1c as many as 12 people in the experimental group (80.0%) was more than the control group as many as 10 people (66.7%). Based on the risk factor of serum uric acid level in the group of the incidence of peripheral diabetic neuropathy was obtained 8 people (53.3%) with high serum uric acid level, it was more than in the group without peripheral paralytic neuropathy that found 4 people with high serum uric acid level (26.7%).

However, there was no statistically significant difference with p=0.136 and odds ratio by 3.143 (95% CI 0.681-14.503) in this study. The result of odds ratio (OR) was more than 1, so then it was concluded that high serum uric acid levels had no correlation with the incidence of diabetic peripheral neuropathy in type 2 diabetes mellitus. It was not in accordance with this research that conducted by Rafie et al against 132 patients with T2DM aged 45-80 years who suggested there was a correlation between high serum uric acid and diabetic peripheral neuropathy in DM patients (p <0.0001).

Next, the difference could be caused by the age of research. The subjects in this study was 40-60 years while the subjects by Rafie et al up to 80 years. In general, the older age also affects the incidence of peripheral diabetic neuropathy. The multicenter study conducted in the UK, the prevalence of diabetic peripheral neuropathy increased with age, from 5% (3.1- 6.9%) in the 20-29 year age group to 44.2% (41.1-47.3%) In the 70-79 age group [17]. The risk factor that affected the DPN was the duration of T2DM.. In the experimental group with T2DM duration ≥5 years more than the control group and statistically significant with p=0.000.

Conclusion

There was no correlation between the high serum uric acid levels and the incidence of diabetic peripheral neuropathy in patients with T2DM in Soetomo General Hospital Surabaya in August until December 2016.

Ethical Clearance: This research involves participants in the survey using sampling method that was accordant with the ethical research principle based on the regulation of research ethic committee. The present study was carried out in accordance with the research principles. This study implemented the basic principle ethics of respect, beneficence, nonmaleficence, and justice.

Conflict of Interest: So far there is no conflict involved with this paper.

Source of Funding: All of the research related with this paper is done by authors' fund only.

References

1. Joeliantina A, Agil M, Qomaruddin MB, Soedirham O. Family Support for Diabetes Self-care Behavior in T2DM Patients who Use Herbs as a Complementary Treatment. Medico-Legal Updat. 2019;19(1).
2. Bonaventura A, Vecchié A, Carbone S, Montecucco F, Abbate A. Comment on Hypoglycemia and hyperglycemia are risk factors for falls in the hospital population by Berra et al. Acta Diabetol. 2019;1–2.
3. Juster-Switlyk K, Smith AG. Updates in diabetic peripheral neuropathy. F1000Research. 2016;5.
4. Feldman EL, Nave K-A, Jensen TS, Bennett DLH. New horizons in diabetic neuropathy: mechanisms, bioenergetics, and pain. Neuron. 2017;93(6):1296–313.
5. Ahsan A, Nursalam N, Efendi F. Model Development of Nursing Service Loyalty. Indian J Public Heal Res Dev. 2019;10(1).
6. Mauline AF, Bramantoro T, Palupi R. Dental Health Behavior in Elderly based on Demographic Characteristics. Indian J Public Heal Res Dev. 2019;10(4).
7. RAMADHAN R, KRISTANTI AN, AMIRTA R, KUSUMA IW, PHUWAPRAISIRISAN P, HAQIQI MT, et al. Screening for potential antidiabetes and antioxidant activities of selected plants from East Kalimantan, Indonesia. Biodiversitas J Biol Divers. 2019;20(7).
8. Graham DY, Miftahussurur M. Helicobacter pylori urease for diagnosis of Helicobacter pylori infection: A mini review. J Adv Res. 2018;13:51–7.
9. Volmer-Thole M, Lobmann R. Neuropathy

and diabetic foot syndrome. Int J Mol Sci. 2016;17(6):917.

10. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of inhaled cannabis on painful diabetic neuropathy. J Pain. 2015;16(7):616–27.
11. Vinik AI. Diabetic sensory and motor neuropathy. N Engl J Med. 2016;374(15):1455–64.
12. Pieruzzi F, Antolini L, Salerno FR, Giussani M, Brambilla P, Galbiati S, et al. The role of blood pressure, body weight and fat distribution on left ventricular mass, diastolic function and cardiac geometry in children. J Hypertens. 2015;33(6):1182–92.
13. Ko M-C, Lin W-H, Martini S, Chang Y-H, Chiu C-T, Li C-Y. A cohort study of age and sex specific risk of pyogenic liver abscess incidence in patients with type 2 diabetes mellitus. Medicine (Baltimore). 2019;98(17):e15366.
14. Putri APS, Hidajah AC. Indicator of Dyslipidemia for Ischemic Stroke in Elderly with Hypertension. Indian J Public Heal Res Dev. 2019;10(3).
15. West RK, Ravona-Springer R, Livny A, Heymann A, Shahar D, Leroith D, et al. Age Modulates the Association of Caffeine Intake With Cognition and With Gray Matter in Elderly Diabetics. Journals Gerontol Ser A. 2018;
16. Soetrisno S, Mulyani S, Nurinasari H, Budi E. The Influence of Psychocurative on Cortisol Level, Anxiety, and Quality of Life in Advanced Stage Cervical Cancer Patients. Folia Medica Indones. 2019;55(3):202–5.
17. Hadiyanti N, Hasmono D, Islam MS. Analysis of Differences of Serum Thromboxane B2 Level after Taking Acetosal in Acute Thrombotic Stroke with Diabetes Mellitus and Non-Diabetes Mellitus. Folia Medica Indones. 2018;54(1):53–8.